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# NEUTRAL ACYLATION (PROTECTION) OF THE INDOLE NITROGEN: A SIMPLE SYNTHESIS OF INDOLE-1-CARBOXYLATES, INDOLE-1-THIOCARBOXYLATES AND INDOLE-1-CARBOXAMIDES

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***Abstract:*** A simple synthesis of indole-1-carboxylates, indole-1-thiocarboxylates and indole-1-carboxamides (1) under neutral conditions is described. 

***Keywords***: indoles; protecting groups; acylation; carbonyl compounds

Protection of the indole nitrogen is a continually studied, necessary event of the heterocycle.[1] Simple protection can be achieved via a variety of methods, but those approaches generally require either acidic or basic reagents and/or conditions. Also, when C3 unsubstituted indoles are used, the regiochemistry of acylation in many of these methods can be equivocal.[2] Use of basic metal salts of indoles to promote N1 acylation has also been extensively exploited, but not without its own set of limitations.[1] The only neutral approach to acylation of the nitrogen of indole was developed by Boger and Patel[2] in which indole-1-carboxylic anhydride was prepared and reacted with an assortment of nucleophiles. However, in this work, only indole itself was used, and two equivalents of indole were needed to form indole-1-carboxylic anhydride. In this communication, we present an alternative approach to the modification and protection of the indole nitrogen: a procedure which is accomplished under neutral conditions which allows an exceptional flexibility of both the indole and nucleophilic component of the reaction.

A recent communication describing the synthesis of tetrasubstituted ureas using 1,1'-carbonyldiimidazole (CDI) demonstrated the ability to isolate the imidazolyl urea distinctly, and use it to form ureas.[3] The similarity of this work to our efforts using 1,1'-carbonyldiimidazole with indoles to form indole-1-carboxamides and indole-1-carboxylates has prompted us to communicate our preliminary results in this area.

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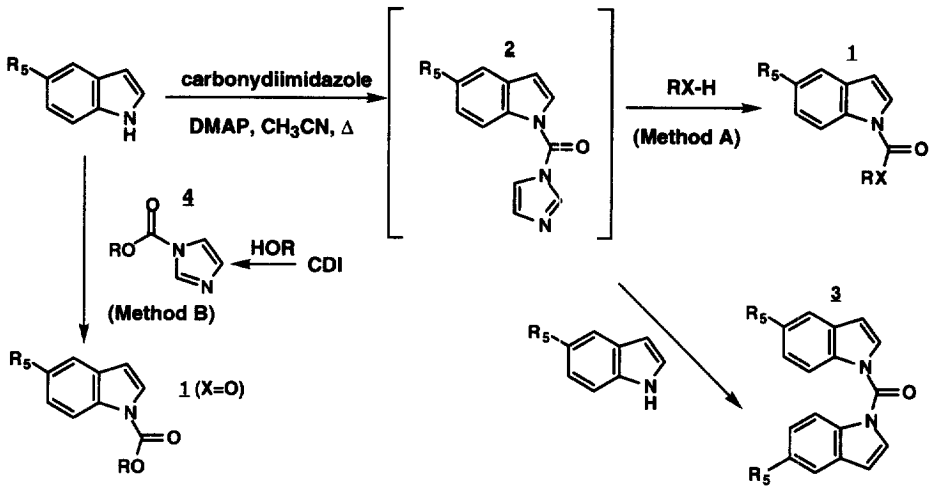
Reaction of the magnesium salt of indole (i.e., basic conditions) with CDI led Snyder and co-workers to conclude that the imidazolyl amide of indole (2) was a compound of limited stability.[4] They reacted 2 with a single amine and isolated the appropriate indole-1-carboxamide in poor yield (38%), suggesting that this approach to indole-1-carboxamides might be of limited value. Synder and co-workers found that the use of thiocarbonyl 1,1'-diimidazole provided the tether they needed for their studies in almost quantitative yield,[4] and they did not pursue the use of CDI further for the synthesis of indole-1-carboxamides.

**Scheme 1**



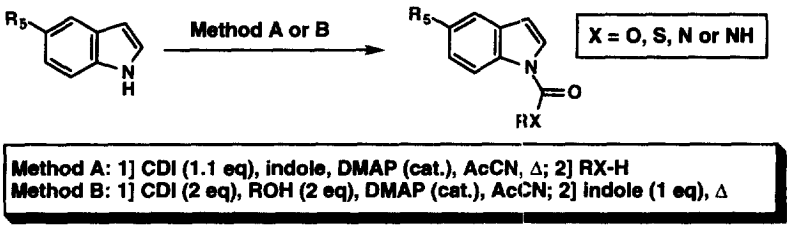

When 2 is formed under our conditions (using DMAP to promote indole nitrogen acylation in acetonitrile at reflux), it is reasonably stable, observable by TLC, but not isolated. Treatment of 2 *in situ* with either amines, alcohols or thiols (RX-H) afforded the desired indole-1-carboxamides, -1-carboxylates, or -1-thiocarboxylates (1, Scheme 1 and Table 1) in varying yields (29-70%, Method A). The conditions of the individual reactions were not optimized. A variety of amines (including an amino acid ester [entry 13]) and alcohols were used in this method. Only a single mercaptan (cyclohexyl mercaptan) was tested. All produced the desired product (Table 1).

During the reaction of indoles with CDI, some of the carbonyl diindole (3, Scheme 1) was formed. In many cases this material could be isolated and characterized. Despite the fact that this material (3) would react with the subsequently added nucleophiles to form the desired product (1), this deleterious reaction pathway lowered the overall yield of the desired reaction since it consumed two molecules of the starting indole. It was therefore not surprising that in all reactions using this method [indole, CDI, then nucleophile - Method A, Table 1], some indole was always recovered. Electron poor indoles (i.e., $R_5$ = -CN) seemed to return the most indole,

whereas electron neutral and electron rich indoles seemed to produce higher yields of the desired product (**1**, Table 1).

With the hope of avoiding this side reaction forming **3**, an alternative approach was taken (Method B, Scheme 1, Table 1). Alcohols reacted with CDI stoichiometrically formed an unstable intermediate carbamate species (**4**) which could in turn be reacted with indoles to formed the desired indole-1-carboxylates (**1**, X=O, 33-90%, Method B). Our initial studies do not reveal whether or not this was a higher yielding approach to indole-1-carboxylates **1** (X=O) compared with Method A (Table 1). However, this alternative approach failed to make indole-1-carboxamides (**1**, X=N), as indoles did not react with the imidazolyl urea species analogous to **4**.

Table 1



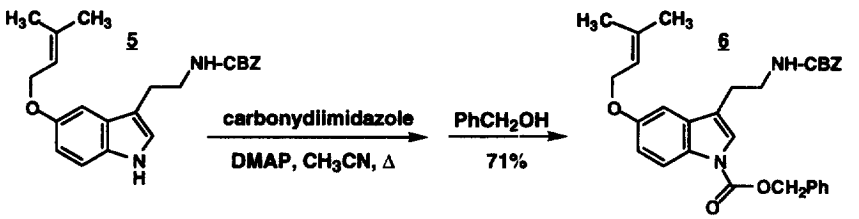

| Example | $R_5$ | RX-H | Method | Yield (%) |
|---|---|---|---|---|
| 1 | -OMe | $PhCH_2OH$ | B | 84 |
| 2 | -OMe | $PhCH_2NH_2$ | A | 70 |
| 3 | -OMe | cyclohexyl-SH | A | 57 |
| 4 | -CN |  | A | 32 |
| 5 | -CN | cyclopentyl-OH | A | 35 |
| 6 | -CN | $CH_3OH$ | A | 53 |
| 7 | -CN | $CH_3OH$ | B | 33 |
| 8 | -H | cyclohexyl-$NH_2$ | A | 60 |
| 9 | -H | PhOH | B | 90 |
| 10 | -H | $CH_3OH$ | A | 41 |
| 11 | -H | $(CH_3)_2CHOH$ | A | 83 |
| 12 | -H | $PhCH_2NH_2$ | A | 48 |
| 13 | -H | alanine, ethyl ester | A | 29 |

*A typical procedure is as follows* (Method A): To a stirred solution of the indole (7.00 mmol) in anhydrous acetonitrile (25 mL) was added 1,1'-carbonyldiimidazole (1.20 g, 7.40 mmol, 1.06 eq) followed by 4-dimethylaminopyridine (DMAP, 20 mg). The resulting solution was stirred at reflux under argon until all indole

was consumed by TLC or 8 h (whichever was shorter). The resulting reaction solution was cooled, the appropriate alcohol, thiol, or amine (10 mmol) was added, and the resulting solution was again heated at reflux under argon overnight (16 h). The resulting reaction was cooled and evaporated under reduced pressure. Crystallization in ethyl acetate (20 mL) or column chromatography afforded the desired compound (1).

This new methodology for the formation of indole-1-carbonyl compounds (1) proved to be useful in one of our approaches for the synthesis of novel serotonergics. In order to carry out the further transformations of a highly substituted serotonin derivative 5, procured by a method previously described,[5] we needed to protect the indole nitrogen under neutral conditions. We were concerned that basic conditions would cause cross-reactivity with the CBZ-NH, and acidic conditions had already proved to cleave the alkenyloxy sidechain. Using the method described in this communication (Method A), the desired N-CBZ-protected indole (6) was prepared under neutral conditions in an unoptimized 71% yield. This result demonstrates the generality of our method, and extends its utility to tryptamine derivatives (i.e., 5).

Scheme 2




In conclusion, we have provided a new, flexible route for the unambiguous synthesis of indole-1-carboxylates, indole-1-carboxamides, and indole-1-thiocarboxylates which is performed under neutral conditions. A wide variety of indoles, amines and alcohols have been used in this reaction, and this approach would appear to be general in nature and applicable to tryptamine derivatives. We continue to explore the optimization of the conditions of this transformation.

**References:**

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